Synthesis B. Schmidt et al. Paper

Stereoselective Synthesis of 2*Z*,4*E*-Configured Dienoates through Tethered Ring Closing Metathesis

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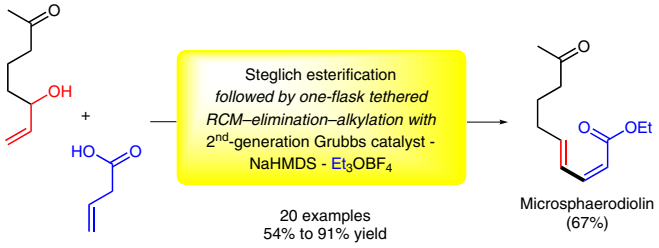


Received: 14.06.2016
Accepted after revision: 19.07.2016
Published online: 31.08.2016
DOI: 10.1055/s-0035-1562536; Art ID: ss-2016-t0430-op

Abstract A two-step sequence leading from racemic allylic alcohols and vinylacetic acid to ethyl (2*Z*,4*E*)-dienoates is described. The sequence involves Steglich esterification of the reactants, followed by a one-pot ring closing metathesis–base induced elimination–alkylation reaction to furnish the products in high stereoselectivity. Trapping of the intermediate sodium carboxylates is accomplished efficiently using Meerwein's salt Et_3OBF_4.

Key words allyl alcohols, dienes, ring closing metathesis, ruthenium, elimination

The stereoselective synthesis of conjugated dienes has attracted considerable attention for many years.[1] A major driving force for the development of methods for their synthesis is the presence of 1,3-dienes in many natural products. Representative examples are macrolactin A, an antiviral marine macrolide with one *E*,*E*- and two *Z*,*E*-diene moieties,[2] and leiodermatolide, a cytotoxic, antimitotic macrolide isolated from a marine sponge, with a *Z*,*Z*- and an *E*,*E*-diene structure (Figure 1).[3]

Commonly used strategies for the stereoselective construction of 1,3-dienes involve Stille or other Pd-catalyzed cross coupling reactions of stereodefined vinyl iodides and vinyl metal compounds, as exemplified in Smith's total synthesis of macrolactin A[4] or Paterson's total synthesis of leiodermatolide.[5] Stereoselective olefination reactions of enals have also been used to access conjugated dienes, for instance by Carreira and co-workers who synthesized the *Z*,*E*-dienoate moiety of macrolactin A via a Still–Gennari olefination[6] or by Maier and co-workers, who used the same reaction in the synthesis of a neopeltolide A analogue.[7] Less common, but synthetically very useful, are *Z*-selective hydrometalation reactions of enynes and the subsequent use of the *E*,*Z*-configured dienyl metal compounds as nucleophiles,[8] or ring closing alkyne metathesis followed by *Z*-selective partial reduction of the alkyne.[9] Recently, the stereospecific electrocyclic ring opening of *trans*- and *cis*-disubstituted cyclobutenes has been established as a powerful method for the stereoselective synthesis of *E*,*E*- and *E*,*Z*-dienes, respectively, for example in the synthesis of the southeast fragment of macrolactin A.[10] Olefin metathesis based approaches to conjugated dienes rely mostly on simpler 1,3-dienes as starting materials, which undergo cross metathesis at the more exposed (or less electron-deficient) double bond.[11–13] It has also been demonstrated that cross metathesis starting from *Z*,*E*-dienes may proceed with conservation of the *Z*-configuration,[14,15] and a *Z*,*E*-configured diene embedded in a macrocycle has been accessed through the ring closing olefin metathesis of a diene substituted with a stereodirecting silyl group.[16] In this context, syntheses of dienes that rely both on olefin metathesis and carbonyl olefination should be mentioned: alkenes have been converted into dienoates via one-pot cross metathesis

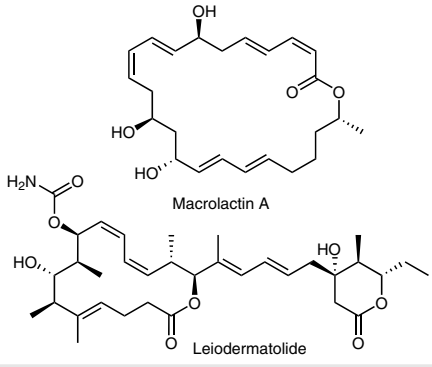
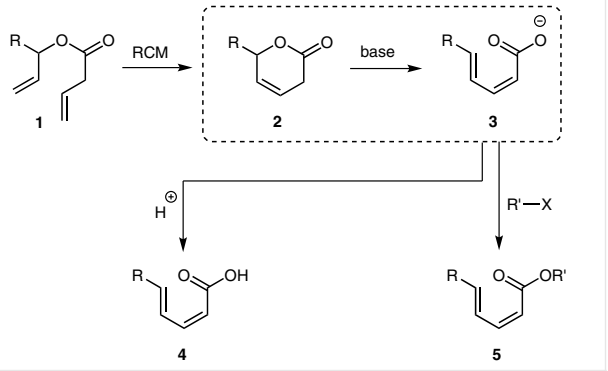


Figure 1 Examples of natural products with conjugated diene structures

with an enal, followed by Wittig olefination with a stabilized ylide[17] or Horner–Wadsworth–Emmons olefination with a phosphonate.[18,19] Murelli and Snapper have disclosed a tandem sequence of cross metathesis and carbonyl olefination with a diazoacetate, in which both C–C bond forming steps are Ru catalyzed. This tandem sequence yields dienoates with high *E*,*E*-selectivity.[20]

Recently, we developed a straightforward and highly stereoselective method for the synthesis of (2*Z*,4*E*)-dienecarboxylic acids that makes use of a tethered ring closing metathesis strategy.[21,22] Tethered RCM is normally used to overcome stereochemical and entropic constraints of cross metathesis reactions by connecting the coupling partners with a labile tether, thereby making the metathesis reaction intramolecular.[23] In most of these transformations, the tether is hydrolytically removed after the metathesis step.[24–27] In our diene synthesis, however, it remains in the target molecule as a carboxylic acid group. The synthesis starts from allyl butenoates **1**, which undergo RCM, followed by base induced elimination to the carboxylates **3**. In previous applications of this method[21,22] we have used an aqueous acidic workup procedure to obtain (2*Z*,4*E*)-diene carboxylic acids **4**. For many synthetic purposes, however, we expect that the corresponding esters **5** are much more conveniently purified and converted into other products than the carboxylic acids **4**. Esterification of carboxylic acids **4** under routine conditions (acid catalyzed or via the acid chlorides) was considered to be risky, because of the isomerization sensitive *Z*-double bond, or not generally applicable, if acid-sensitive functional groups are present. To access the desired (2*Z*,4*E*)-dienoates directly from the tethered RCM, we investigated a variant of our previously published method that involves trapping of the carboxylates **3** with an alkylating agent R′-X (Scheme 1). Herein we report the extension of the RCM–base induced ring opening sequence by an alkylation step and the methodological improvements and modifications that were required to accomplish this goal.



Scheme 1 Synthesis of diene carboxylic acids **4** (previous work) and esters **5** (this work) via tethered RCM

Initially, the optimized conditions for the tethered RCM–base induced ring opening sequence were used. RCM of **1a** (R = Ph) was accomplished in toluene at elevated temperature with catalyst **A**,[28] followed by addition of NaH to induce the eliminative ring opening. Instead of an aqueous acidic workup, we then added methyl iodide to alkylate the intermediate Na-carboxylate **3a**, but to no avail. Even with a large excess of methyl iodide and under reflux conditions we were unable to detect any traces of the desired methyl ester **5** (see Scheme 1, R = Ph, R′ = Me). There is precedence for the alkylation of carboxylates with methyl iodide, but in most examples polar aprotic solvents,[29] such as DMF or DMSO, which are incompatible with olefin metathesis reactions, are used. Therefore, we sought for a more electrophilic alkylating agent that might be used in typical olefin metathesis solvents, such as toluene or dichloromethane. Gratifyingly, triethyloxonium tetrafluoroborate, commonly known as Meerwein's salt,[30,31] gave the desired ester **5a** in toluene with an acceptable yield of 67%, based on butenoate **1a** (Table 1, entry 1). In the next step we tested THF as a solvent for the one-pot procedure, because we expected that both the base induced elimination and the alkylation of the carboxylate should proceed faster and with higher conversions in a more polar solvent. On the other hand, THF is not a solvent of choice for olefin metathesis reactions, although it has occasionally been used in special circumstances.[32,33] When we repeated the RCM–base induced ring opening–alkylation sequence of **1a** in THF at 60 °C under otherwise identical conditions, the ethyl dienoate **5a** was obtained in virtually the same yield, but in perceptibly shorter reaction times. While the time required for the metathesis step was hardly affected by the solvent switch (ca. 1 h for THF and toluene), base induced elimination (ca. 1 h in THF vs. 6 h in toluene) and alkylation (ca. 0.5 h in THF vs. 3 h in toluene) were significantly faster in the more polar solvent, as anticipated (entry 2). The overall yield of **5a** in THF is satisfactory, but we observed the formation of a highly polar, presumably polymeric, material in this solvent. We assume that this polymer is formed through the well known cationic ring opening polymerization of THF initiated by Meerwein's salt.[34] Although chromatographic removal of the highly polar byproduct is not a problem, we reasoned that a competing polymerization of the solvent would consume the alkylating agent and lower the yield of the desired product. For this reason, and to avoid isolation problems that might occur with more volatile products in toluene, we investigated dichloromethane as a solvent for the one-pot sequence. Not unexpectedly, this solvent reacted vigorously and highly exothermic with NaH (entry 3), whereas butyllithium induced a decomposition of the intermediate RCM product, presumably through uncontrollable nucleophilic addition to the carbonyl group (entry 4). Eventually, NaHMDS, used as a 1 M solution in THF, was identified as a suitable base. Upon addition of Meerwein's salt the ethyl ester **5a** could be isolated in an improved yield of 74% (entry

5). Similarly, the 4-bromophenyl derivative **5b** was obtained from **1b** (entries 6–8), and the 2-fluorophenyl derivative **5c** from **1c** (entries 9 and 10). A remarkable difference was observed for the MOM- and TBS-protected *o*-phenols **1d** and **1e**. While the MOM-protected derivative **5d** could be isolated in an acceptable yield of 54% (entry 11), the TBS analogue **1e** failed to undergo RCM under the standard conditions, probably due to the sterically demanding protecting group. For this example, the starting butenoate was recovered unchanged (entry 12). We next applied the RCM–base induced ring opening–alkylation conditions to butenoates with aliphatic substituents R. The TBS ether **1f** was cleanly converted into **5f** under all conditions, without any cleavage or scrambling of the TBS protecting group (entries 13–15). For the benzylic MOM derivative **1g** good yields of the expected dienoate **5g** were obtained with NaH, both in toluene and in THF (entries 16 and 17), whereas the yields of **5h**, with a silyloxy allyl side chain, were mediocre in toluene and low in THF (entries 18 and 19). All other examples were successfully performed in CH_2Cl_2 with NaHMDS as the base, with the exception of ketone **1q** (entry 28), which did not undergo RCM but was recovered unchanged. Literature precedence for catalyst inhibition by RCM substrates with carbonyl groups in the side chain exists. For example, Fürstner and Langemann[35] reported that the success of RCM reactions leading to macrocyclic carbonyl compounds strongly depends on the distance between the alkene and the carbonyl group. If the formation of a stable five- or six-membered chelate is possible, as for example with starting material **1q**, the catalytic cycle may be interrupted (Figure 2).

To overcome the presumed catalyst inhibition and to test the feasibility of the RCM–base induced ring opening–alkylation sequence for a substrate with a second enolizable group, the butenoate **1r** with a *tert*-butyl ester in the side chain was subjected to standard conditions C as stated in Table 1.

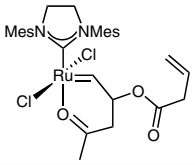
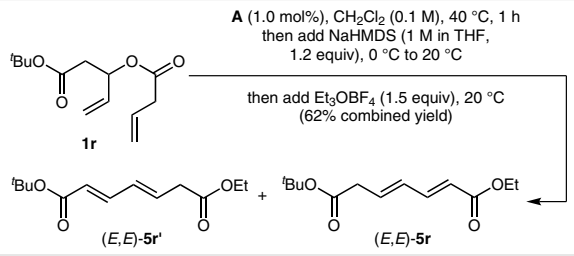


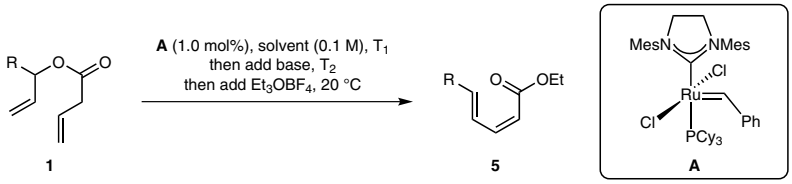
Figure 2 Proposed catalyst inhibition by the pending carbonyl group in **1q**

In contrast to **1q** this substrate readily undergoes RCM, presumably because inhibitive chelation is suppressed by the steric bulk of the *tert*-butyl group, but the base induced ring opening–alkylation step results in the formation of a 1:1 mixture of *E*,*E*-configured dienes **5r** and **5r'** (Scheme 2). The observation that no *Z*-configured double bonds are present in these products suggests that after the ring opening step a base mediated equilibration to a mixture of the thermodynamically more stable dienes occurs.



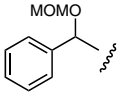
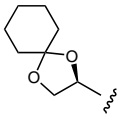
Scheme 2 RCM–base induced ring opening–alkylation sequence for **1r** with a second enolizable group

Table 1 Synthesis of (2*E*,4*Z*)-Dienecarboxylic Acid Esters via RCM–Base Induced Ring Opening–Alkylation Sequence



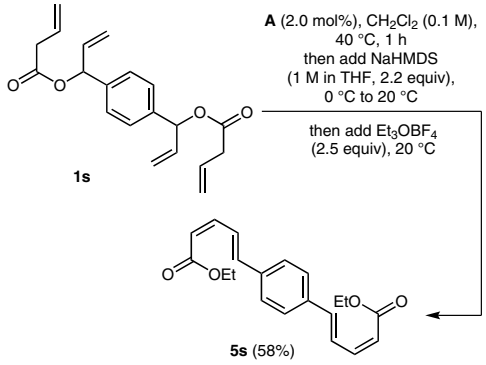
Entry	1	R	Solvent	Base	Conditions[a]	Product	Yield (%)
1			toluene	NaH	A	**5a**	67
2			THF	NaH	B	**5a**	65
3	**1a**[21]	Ph	CH_2Cl_2	NaH	C	**5a**	–[b]
4			CH_2Cl_2	BuLi	C	**5a**	–[c]
5			CH_2Cl_2	NaHMDS	C	**5a**	74

Table 1 (continued)

Entry	1	R	Solvent	Base	Conditions[a]	Product	Yield (%)
6			toluene	NaH	A	**5b**	44
7	**1b**[21]	4-BrC_6H_4	THF	NaH	B	**5b**	54
8			CH_2Cl_2	NaHMDS	C	**5b**	62
9			toluene	NaH	A	**5c**	75
10	**1c**[21]	2-FC_6H_4	THF	NaH	B	**5c**	65
11	**1d**	2-$MOMOC_6H_4$	CH_2Cl_2	NaHMDS	C	**5d**	54
12	**1e**	2-$TBSOC_6H_4$	CH_2Cl_2	NaHMDS	C	**5e**	–[d]
13			toluene	NaH	A	**5f**	72
14	**1f**[21]		THF	NaH	B	**5f**	75
15			CH_2Cl_2	NaHMDS	C	**5f**	82
16			toluene	NaH	A	**5g**	69
17	**1g**[21]		THF	NaH	B	**5g**	75
18			toluene	NaH	A	**5h**	57
19	**1h**[21]		THF	NaH	B	**5h**	27
20	**1i**[21]	CH_2CH_2Ph	CH_2Cl_2	NaHMDS	C	**5i**	76
21	**1j**[21]	Pr	CH_2Cl_2	NaHMDS	C	**5j**	68
22	**1k**[21]	CH_2CHMe_2	CH_2Cl_2	NaHMDS	C	**5k**	65
23	**1l**[21]	$(CH_2)_4Me$	CH_2Cl_2	NaHMDS	C	**5l**	91
24[e]	**1m**	CH_2OTBS	CH_2Cl_2	NaHMDS	C	**5m**	77
25	**1n**		CH_2Cl_2	NaHMDS	C	**5n**	80
26	**1o**		CH_2Cl_2	NaHMDS	C	**5o**	84
27[f]	**1p**	$SiMe_3$	CH_2Cl_2	NaHMDS	C	**5p**	79
28	**1q**		CH_2Cl_2	NaHMDS	C	**5q**	–[d]

[a] *Conditions A*: 1. **A** (1.0 mol%), toluene (0.1 M), 80 °C, 1 h; 2. NaH (60 wt% dispersion in mineral oil, 1.5 equiv), 80 °C, 6 h; 3. Et_3OBF_4 (1.3 equiv), 0 °C to 20 °C, 3 h. *Conditions B*: 1. **A** (1.0 mol%), THF (0.1 M), 60 °C, 1 h; 2. NaH (60 wt% dispersion in mineral oil, 1.5 equiv), 60 °C, 1 h; 3. Et_3OBF_4 (1.3 equiv), 0 °C to 20 °C, 0.5 h. *Conditions C*: 1. **A** (1.0 mol%), CH_2Cl_2 (0.1 M), 40 °C, 2 h; 2. NaHMDS (1 M in THF, 1.2 equiv, except for entries 3 and 4), 0 °C to 20 °C, 3 h; 3. Et_3OBF_4 (1.5 equiv), 20 °C, 6 h.
[b] Vigorous decomposition of the solvent.
[c] Decomposition of the starting material.
[d] No conversion in RCM.
[e] 2.0 mol% of catalyst **A** were required.
[f] 1.3 mol% of catalyst **A** were required.

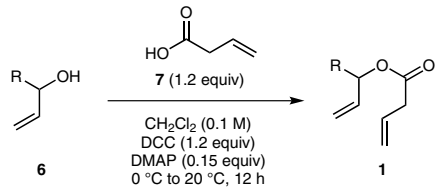
Finally, a twofold RCM–base induced ring opening–alkylation sequence was tested for tetraene **1s**, which was derived from terephthalic aldehyde. Subjecting **1s** to conditions C (see Table 1) with double amounts of catalyst **A** furnished **5s** in fair yield (Scheme 3).



Scheme 3 Twofold RCM–base induced ring opening–alkylation sequence of **1s**

All starting materials **1** required for the RCM–base induced ring opening–alkylation sequence were synthesized from allylic alcohols **6** and vinylacetic acid (**7**) by Steglich esterification.[36] For all previously described butenoates, a reference is provided in Table 1. The yields and possibly deviations from the standard protocol for all others are listed in Table 2, along with references for the allylic alcohols **6**.

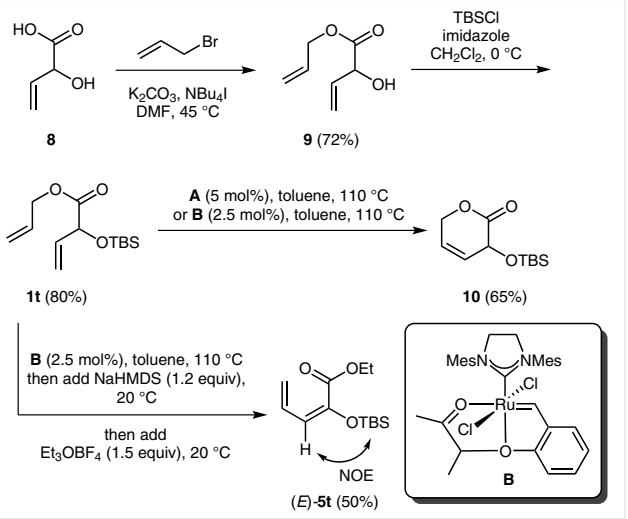
Table 2 Syntheses of Hitherto Unknown Butenoates



Entry	Substrate **6**	Product **1**	Yield (%)
1	**6d**[a]	**1d**	64
2	**6e**[a]	**1e**	57
3	**6m**[37]	**1m**	85
4	**6n**[a]	**1n**[b]	93
5	**6o**[38]	**1o**[b]	64
6	**6p**[39]	**1p**	70
7	**6q**[40]	**1q**	70
8	**6r**[41]	**1r**	69
9[c]	**6s**[42]	**1s**	84

[a] New compound, see Supporting Information for details.
[b] Mixture of diastereomers.
[c] Double amount of **7**, DCC, and DMAP.

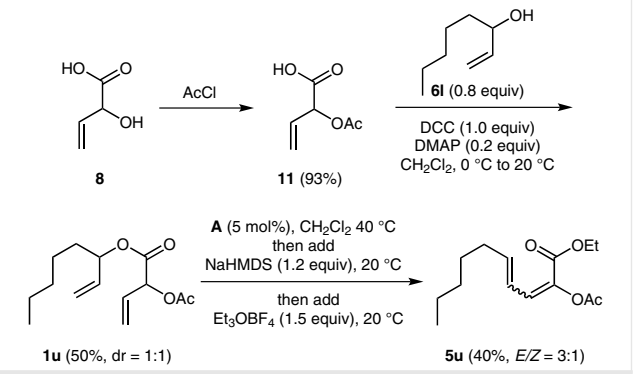
In the next step we aimed at an expansion of the substrate scope by investigating the RCM–base induced ring opening–alkylation sequence for α-substituted butenoates. To this end, vinylglycolic acid (**8**), prepared via the cyanohydrin of acrolein as described previously,[43] was converted into its allyl ester **9** under mildly basic conditions, followed by protection of the hydroxy group as its TBS ether to give **1t**. We first investigated conditions for the RCM of **1t** and found that, compared to the standard conditions, a fivefold increased amount of second generation Grubbs catalyst **A** is required for quantitative conversion. Our recent positive experiences[22,44] with the Umicore M51 catalyst (**B**)[45] prompted us to test this Ru-alkylidene in the RCM of **1t**. Gratifyingly, full conversion of **1t** to **10** was accomplished with a notably reduced catalyst loading of 2.5 mol% under otherwise identical conditions. Applying the conditions of the RCM–base induced ring opening–alkylation sequence with toluene as a solvent and **B** as the catalyst furnished diene **5t** as a 3:1 mixture of *E*/*Z*-isomers. By repeated chromatography, the major isomer, (*E*)-**5t**, could be isolated in sufficient purity to allow structure elucidation by 2D-NOE spectroscopy. A cross peak between the signals of the TBS group and H3 is indicative for the assigned double bond configuration (Scheme 4).



Scheme 4 Synthesis of precursor **1t** and its RCM–base induced ring opening–alkylation to **5t**

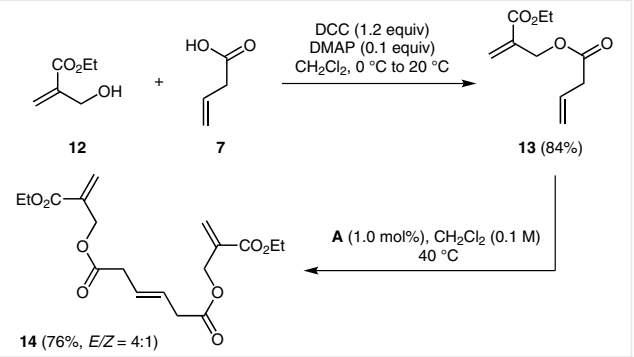
Vinylglycolic acid (**8**) was also used as a starting material for the synthesis of a precursor **1u**, which was required to test the accessibility of 2,5-disubstituted dienoates. Acetylation of **8**, followed by Steglich esterification with allyl alcohol **6l** furnished **1u**, which indeed underwent the RCM–ring opening–alkylation sequence to **5u**, albeit in low yield and diastereoselectivity (Scheme 5).

We also investigated the possibility to synthesize dienoates with a substituent at the 4-position. To this end, allylic alcohol **12**, synthesized via Morita–Baylis–Hillman re-



Scheme 5 Synthesis of precursor **1u** and its RCM–base induced ring opening–alkylation to **5u**

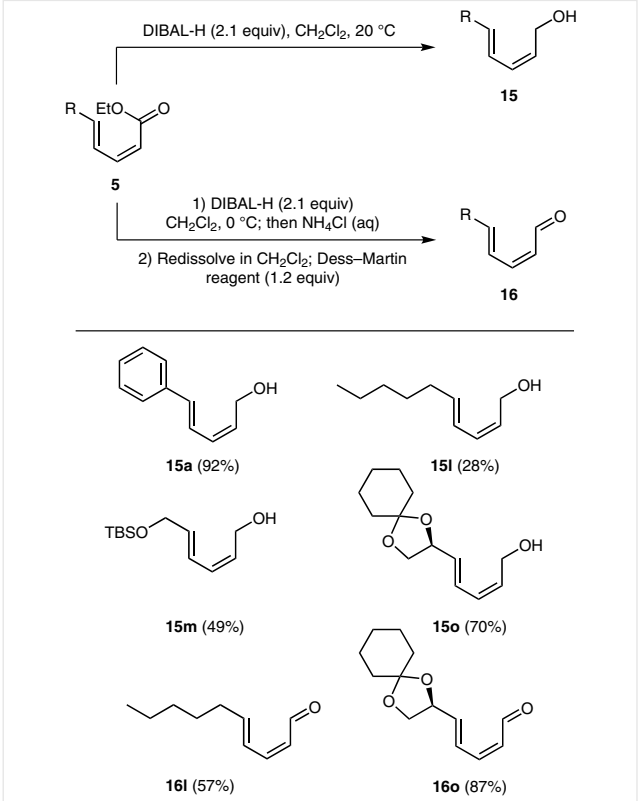
action as described previously,[46] was converted into the butenoate **13**. Under the standard olefin metathesis conditions this precursor did not undergo RCM, but a clean self metathesis to the dimer **14**, which was isolated as a 4:1 mixture of *E*- and *Z*-isomers (Scheme 6).



Scheme 6 Synthesis of precursor **13** and attempted RCM

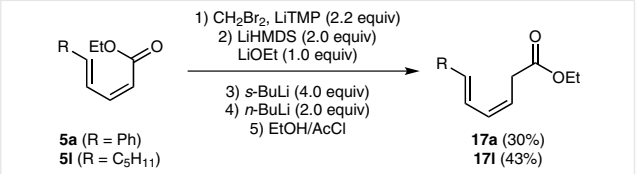
With these somewhat mixed results in hand, we decided not to pursue further investigations into the expansion of substitution patterns compatible with the RCM–ring opening–alkylation sequence. Instead, we investigated the chemoselectivity of some transformations of the ethyl dienoates **5** with a view to possible applications in target molecule synthesis. We were particularly interested to check the stereochemical integrity of the *Z*,*E*-configured diene under conditions required for the reduction of the ester group (Scheme 7).

For the esters **5a**, **5l**, **5m**, and **5o** reduction to the (2*Z*,4*E*)-configured pentadienols **15** was accomplished with conservation of the *Z*,*E*-configuration of the diene. The alcohols **15** are only moderately stable upon workup and purification by column chromatography on silica gel, which might explain the variable yields. Oxidation of **15l** with MnO_2 gave the expected aldehyde **16l**, but with concomitant partial isomerization to the *E*,*E*-configured pentadienal. With the Dess–Martin periodinane[47] the *Z*,*E*-configuration of the diene was maintained. An improved overall yield of **16l** could be obtained when the intermediate alcohol **15l** was not exposed to strongly acidic conditions during workup and immediately subjected to Dess–Martin oxidation without further purification. Via the same protocol, pentadienal **16o** was synthesized in 87% yield.



Scheme 7 Reduction of dienoates **5** to pentadienols **15** and reduction–oxidation of dienoates **5** to pentadienals **16** without isolation of the alcohols

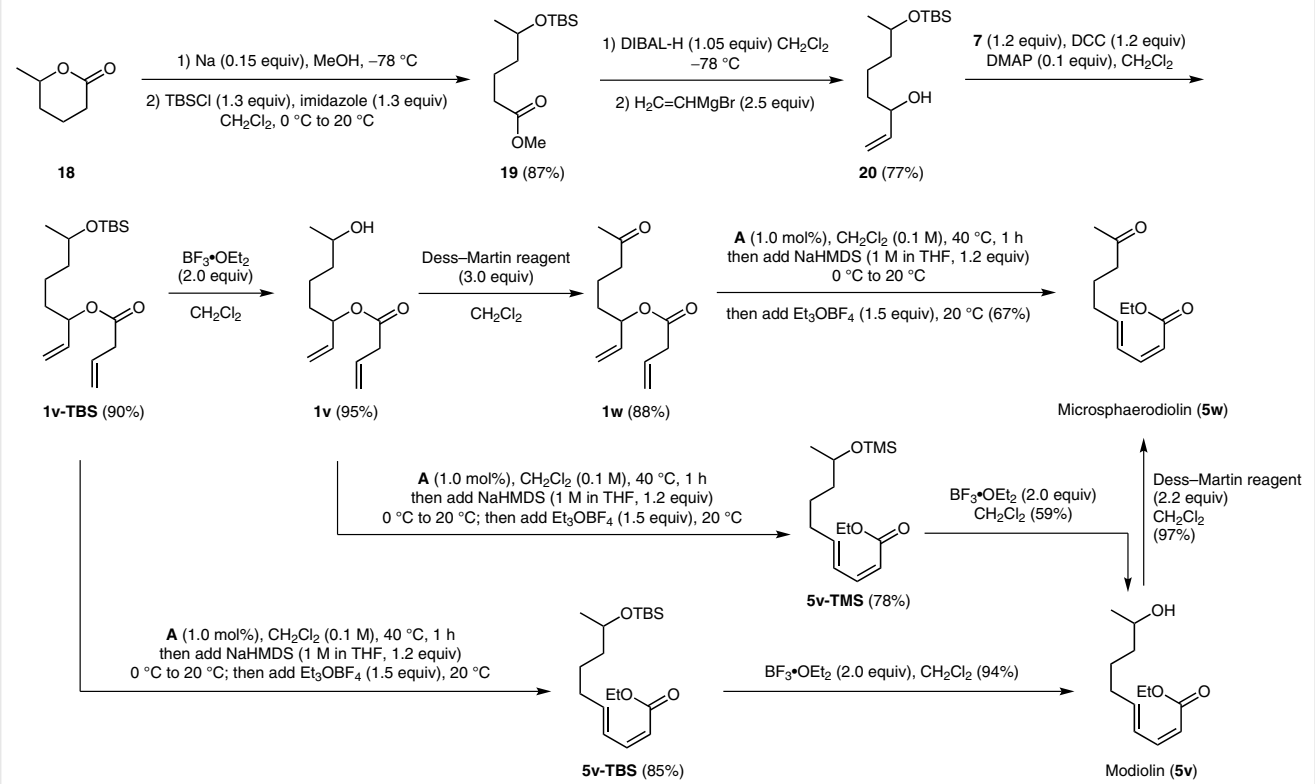
A potentially very useful transformation of *Z*,*E*-configured dienoates is Kowalski's homologation,[48–50] which would result in a separation of the diene and the carboxylate by an additional methylene group (Scheme 8). It has been shown that this reaction can be applied to (*Z*)-cinnamates with retention of the double bond configuration, but to the best of our knowledge it has not been applied to dienoates. Kowalski's homologation starts with the nucleophilic addition of $LiCHBr_2$ to the ester group, followed by a complex series of halogen–metal exchange, deprotonation, rearrangement to an ynolate, and its protonation to a ketene, which is eventually trapped by ethanol to furnish the ester. We applied Kowalski's improved conditions[50] to dienoates **5a** and **5l**. For both examples the reaction proceeded to the (3*Z*,5*E*)-configured dienes **17a** and **17l**, respectively, but unfortunately only in poor to moderate yields.



Scheme 8 Kowalski homologation of dienoates **5a** and **5l**

Ethyl esters are by no means uncommon structural elements in compounds isolated from natural sources, although it should be taken into account that some naturally occurring ethyl esters might be artifacts, resulting from reactions of the actual natural products with the solvent used during isolation or purification.[51] While several ethyl dienoates have been synthesized for medicinal chemistry purposes, e.g. for evaluation as antiviral agents[52] or as monoamine oxidase inhibitors,[53] only a few compounds have been reported as natural products.[54,55] Two (2*Z*,4*E*)-configured ethyl dienoates from natural sources are modiolin (**5v**), isolated from the fungus *Paraphaeosphaeria* sp.,[56] and microsphaerodiolin (**5w**), isolated from the fungus *Microsphaeropsis arundinis*.[57] The synthesis of both compounds started from δ-methyl-δ-valerolactone (**18**), which was cleaved with sodium methoxide and OH-protected to give the methyl ester **19**.[58] One-pot reduction–Grignard addition furnished the allylic alcohol **20**, which was then acylated under Steglich conditions to give the TBS-protected modiolin precursor **1v-TBS**. Deprotection of **1v-TBS** gave the unprotected butenoate **1v**, which was oxidized with Dess–Martin periodinane to the microsphaerodiolin precursor **1w**.

Application of the standard RCM–base induced ring opening–alkylation conditions to **1v-TBS** furnished TBS-protected *rac*-modiolin **5v-TBS** without complications in high yield, which was deprotected to *rac*-modiolin (**5v**). We also subjected **1v** with a free secondary alcohol to the standard conditions and found that not modiolin (**5v**) is the product, as expected, but that its TMS ether **5v-TMS** was isolated in high yield. We assume that NaHMDS first deprotonates the alcohol, and that a trimethylsilyl group is then transferred from $HN(SiMe_3)_2$ to the alkoxide, generating a new base $NaNHSiMe_3$, which could promote the base induced ring opening. Modiolin (**5v**) was obtained from **5v-TMS** via Lewis acid mediated desilylation. Microsphaerodiolin (**5w**) was synthesized from ketone **1w** under standard conditions and from modiolin (**5v**) by oxidation of the secondary alcohol. Notably, in contrast to ketone **1q** (Table 1, entry 28), the RCM of **1w** proceeds smoothly, because coordination of the carbonyl oxygen to the catalytically active Ru center would result in the formation of a rather unstable eight-membered chelate complex (Scheme 9).



Scheme 9 Syntheses of modiolin (**5v**) and microsphaerodiolin (**5w**) via RCM–base induced ring opening–alkylation of precursors **1v-TBS**, **1v**, and **1w**

In summary, we describe a short and highly stereoselective route to (2*Z*,4*E*)-dienoic esters that proceeds in one pot through a tethered olefin metathesis reaction, an eliminative ring opening, and the final alkylation of the resulting Na-carboxylate with Meerwein's salt. Scope and limitations of the method have been evaluated, and it has been applied to the synthesis of two ethyl dienoates from natural sources.

All experiments were conducted, unless otherwise stated, using standard Schlenk technique under an atmosphere of dry N_2. CH_2Cl_2, Et_2O, MeOH, and toluene were purified with a solvent purification system. ^{1}H NMR spectra were obtained at 300 MHz, 500 MHz, or 600 MHz in $CDCl_3$ with residual $CHCl_3$ (δ = 7.26) as an internal standard. Whenever the individual lines of a signal (e.g., 'd' or 'dd') show a visible, but, insufficiently resolved fine splitting these signals are described as doublet of multiplets ('dm' or 'ddm'). In these cases only the clearly assignable coupling constants are reported. ^{13}C NMR spectra were obtained at 75 MHz or at 126 MHz with $CDCl_3$ (δ = 77.16) as an internal standard. IR spectra were recorded as ATR-FTIR spectra. Low- and high resolution mass spectra were obtained by EI-TOF or ESI-TOF. Reagents and starting materials were purchased and used as received, unless otherwise stated.

Tethered RCM–Base Induced Ring Opening–Alkylation Sequence; General Procedure

Conditions A or B: To a solution of the corresponding butenoate **1** (1.0 equiv) in dry and degassed toluene (conditions A, 0.1 M) or in dry and degassed THF (conditions B, 0.1 M) was added 2nd generation Grubbs catalyst **A** (1.0 mol%). The solution was heated to 80 °C (conditions A) or to 65 °C (conditions B) until the starting material was fully consumed, as indicated by TLC (0.5–1 h). NaH (60 wt% dispersion in mineral oil, 1.5 equiv) was added, and heating of the mixture to the respective temperature was continued until the intermediate RCM product was fully consumed (TLC, 0.5–6 h). The mixture was then cooled to 0 °C and Et_3OBF_4 (1.3 equiv) was added. It was allowed to warm to r.t. and stirring was continued until full conversion of the carboxylate (TLC, 0.5–3 h). The reaction was quenched by addition of water, diluted with MTBE, and the organic layer was separated. The aqueous layer was extracted with MTBE, the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography (silica, hexane/MTBE mixtures of increasing polarity) to furnish the corresponding ethyl dienoate **5**.

Conditions C: To a solution of the corresponding butenoate (1.0 equiv) in dry and degassed CH_2Cl_2 (0.1 M) was added 2nd generation Grubbs catalyst **A** (1.0 mol%). The solution was heated at 40 °C until the starting material was fully consumed, as indicated by TLC (0.5–2 h). The solution was cooled to 0 °C and NaHMDS (1 M solution in THF, 1.2 equiv) was added. The reaction was stirred at r.t. until the intermediate RCM product was fully consumed (TLC, 2–3 h). Et_3OBF_4 (1.5 equiv) was added and the mixture was stirred at r.t. until full conversion was observed (TLC, 3–6 h). The mixture was dry-loaded on silica gel and purified by column chromatography (silica gel, hexane/MTBE mixtures of increasing polarity) to furnish the corresponding ethyl dienoate **5**.

Ethyl (2*Z*,4*E*)-5-(2-Fluorophenyl)penta-2,4-dienoate (5c)

Following the general procedures: *conditions A*, **1c** (110 mg, 0.50 mmol) was converted into **5c** (82 mg, 0.37 mmol, 75%); *conditions B*, **1c** (110 mg, 0.50 mmol) was converted into **5c** (72 mg, 0.33 mmol, 65%); colorless oil.

IR (ATR): 2983 (w), 2903 (w), 1708 (s), 1622 (s), 1485 (m), 1176 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (ddd, *J* = 15.9, 11.3, 1.0 Hz, 1 H), 7.64 (td, *J* = 7.6, 1.7 Hz, 1 H), 7.30–7.22 (m, 1 H), 7.15–7.05 (2 H), 7.01 (d, *J* = 15.9 Hz, 1 H), 6.75 (t, *J* = 11.3 Hz, 1 H), 5.76 (d, *J* = 11.3 Hz, 1 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 160.8 (d, *J* = 251.5 Hz), 144.4, 144.3, 132.7 (d, *J* = 3.9 Hz), 130.2 (d, *J* = 8.6 Hz), 127.7 (d, *J* = 3.1 Hz), 126.9 (d, *J* = 4.5 Hz), 124.3 (d, *J* = 3.5 Hz), 118.4, 115.8 (d, *J* = 22.0 Hz), 60.0, 14.3.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{13}O_2F$: 220.0900; found: 220.0907.

Ethyl (*S*,2*Z*,4*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]hepta-2,4-dienoate (5f)

Following the general procedures: *conditions A*, **1f** (142 mg, 0.50 mmol) was converted into **5f** (102 mg, 0.36 mmol, 72%); *conditions B*, **1f** (142 mg, 0.50 mmol) was converted into **5f** (107 mg, 0.38 mmol, 75%); *conditions C*, **1f** (284 mg, 1.00 mmol) was converted into **5f** (234 mg, 0.82 mmol, 82%); yellow oil.

$[\alpha]_D^{22}$ +1.9 (*c* 0.64, CH_2Cl_2).

IR (ATR): 2956 (w), 2929 (w), 2857 (w), 1717 (m), 1255 (w), 1182 (s), 1148 (s), 830 (m), 776 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 15.3, 11.4 Hz, 1 H), 6.54 (dd, *J* = 11.4, 11.4 Hz, 1 H), 6.01 (dd, *J* = 15.4, 5.7 Hz, 1 H), 5.63 (d, *J* = 11.4 Hz, 1 H), 4.43 (dq, *J* = 6.1, 6.1 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 148.0, 144.4, 124.7, 117.6, 69.0, 60.1, 26.0, 24.3, 18.4, 14.5, –4.4, –4.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_3SiNa$: 307.1700; found: 307.1713.

Ethyl (2*Z*,4*E*)-5-[(*S*)-1,4-Dioxaspiro[4.5]decan-2-yl]penta-2,4-dienoate (5o)

Following the general procedure: *conditions C*, **1o** (266 mg, 1.00 mmol) was converted into **5o** (224 mg, 0.84 mmol, 84%); yellow oil.

$[\alpha]_D^{27}$ –17.7 (*c* 0.91, CH_2Cl_2).

IR (ATR): 2943 (w), 2862 (w), 1714 (m), 1645 (w), 1604 (w), 1179 (s), 1162 (s), 1096 (s), 845 (m), 820 (m), 700 (w), 657 cm^{-1} (w).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 15.4, 11.4 Hz, 1 H), 6.55 (dd, *J* = 11.4, 11.4 Hz, 1 H), 5.97 (dd, *J* = 15.4, 7.4 Hz, 1 H), 5.69 (d, *J* = 11.3 Hz, 1 H), 4.64 (q, *J* = 6.8 Hz, 1 H), 4.22–4.09 (m, 3 H), 3.63 (t, *J* = 7.8 Hz, 1 H), 1.68–1.55 (m, 8 H), 1.44–1.35 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 143.3, 140.2, 128.8, 119.0, 110.5, 76.1, 69.0, 60.2, 36.4, 35.5, 25.3, 24.1, 24.0, 14.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1403.

Ethyl (2*Z*,4*E*)-5-(Trimethylsilyl)penta-2,4-dienoate (5p)

Following the general procedure: *conditions C*, using **A** (1.3 mol%), **1p** (240 mg, 1.21 mmol) was converted into **5p** (190 mg, 0.96 mmol, 79%); yellow oil.

IR (ATR): 2956, (w), 1716 (m), 1619 (w), 1566 (w), 1248 (m), 1202 (m), 1165 (s), 1010 (m), 848 (s), 837 (s), 748 (m), 712 (m), 694 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (ddd, *J* = 18.4, 10.8, 0.9 Hz, 1 H), 6.56 (dd, *J* = 11.1, 11.1 Hz, 1 H), 6.29 (dd, *J* = 18.4, 0.7 Hz, 1 H), 5.67 (d, *J* = 11.4 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 0.15 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 146.7, 145.8, 139.6, 117.9, 60.2, 14.4, –1.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{19}O_2Si$: 199.1149; found: 199.1149.

Diethyl (2*Z*,2′*Z*,4*E*,4′*E*)-5,5′-(1,4-Phenylene)bis(penta-2,4-dienoate) (5s)

Following the general procedure: *conditions C*, catalyst **A** (17 mg, 2.0 mol%), NaHMDS (2.2 mL, 1 M solution in THF, 2.2 mmol), and Et_3OBF_4 (500 mg, 2.50 mmol), **1s** (326 mg, 1.00 mmol) was converted into **5s** (190 mg, 0.58 mmol, 58%); yellow solid; mp 129–130 °C.

IR (ATR): 2981 (w), 1708 (s), 1621 (m), 1368 (w), 1241 (m), 1176 (s), 1133 (m), 1032 (m), 998 (m), 810 cm^{-1} (w).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.17 (ddd, *J* = 15.7, 11.4, 1.0 Hz, 2 H), 7.49 (s, 4 H), 6.79 (d, *J* = 15.7 Hz, 2 H), 6.73 (dd, *J* = 11.5, 11.5 Hz, 2 H), 5.73 (d, *J* = 11.2 Hz, 2 H), 4.23 (q, *J* = 7.1 Hz, 4 H), 1.33 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.7, 144.7, 140.5, 137.1, 128.0, 125.6, 117.9, 60.2, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}O_4$: 327.1591; found: 327.1611.

Ethyl (2*Z*,4*E*)-9-Oxodeca-2,4-dienoate (Microsphaerodiolin, 5w)

Following the general procedure: *conditions C*, **1w** (140 mg, 666 µmol) was converted into **5w** (95.0 mg, 446 µmol, 67%); colorless oil.

IR (ATR): 2938 (w), 1708 (s), 1637 (m), 1600 (m), 1421 (m), 1365 (m), 1177 (s), 1030 (m), 964 (m), 820 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, *J* = 15.3, 11.3 Hz, 1 H, H-4), 6.52 (dd, *J* = 11.3, 11.3 Hz, 1 H, H-3), 5.99 (dt, *J* = 15.2, 7.0 Hz, 1 H, H-5), 5.57 (d, *J* = 11.3 Hz, 1 H, H-2), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2), 2.43 (dd, *J* = 7.3 Hz, 2 H, H-8), 2.20 (dt, *J* = 7.3, 7.0 Hz, 2 H, H-6), 2.12 (s, 3 H, H-10), 1.72 (tt, *J* = 7.4, 7.4 Hz, 2 H, H-7), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.6 (C-9), 166.6 (C-1), 145.0 (C-3), 144.1 (C-5), 127.8 (C-4), 116.2 (C-2), 60.0 (OCH_2), 42.9 (C-8), 32.4 (C-6), 30.1 (C-10), 22.8 (C-7), 14.4 (OCH_2CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}O_3$: 211.1329; found: 211.1330; *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_3Na$: 233.1148; found: 233.1175.

Anal. Calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.5; H, 8.6. Found: C, 68.0; H, 8.4.

Acknowledgment

Generous financial support of this work by the Deutsche Forschungsgemeinschaft (DFG-grant Schm 1095/6-2) is gratefully acknowledged. We thank Evonik-Oxeno for donations of solvents.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562536.

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